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Family survey of Reiter's disease*

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Some workers have thought that Reiter's disease is due to an agent which enters the body through inflamed mucous membrane, either intestinal or urethral. A simple acute infection, however, would seem unlikely, since in recurrent attacks no urethral infection is found in half the cases and only half of the cases of venereally-acquired urethritis lead to recurrences in patients with past Reiter's disease (Csonka, 1960). The urethritis associated with Reiter's disease and that not so associated appear indistinguishable.

Doubt has been thrown on the infective cause even of the urethritis, since Reiter's syndrome has been produced in rats by injections of Freund's adjuvant (Lacapère, Cohen, Daguet, Delga, Goullet, Marche, Pasquier, and Seman, 1964).

As in other forms of polyarthritis, an autoimmune hypothesis has been suggested and, in the case of Reiter's disease, there is some evidence for the validity of such a theory.

Grimble (1963) found that the serum of 96 per cent. of patients with Reiter's disease reacted to antigens from the prostate gland but only 19 per cent. to antigens from liver or kidney. Patients with ankylosing spondylitis showed a reaction to prostatic antigens in every instance but to liver and kidney antigens in only 25 per cent. Only 11 per cent. of rheumatoid sera reacted with prostatic antigen. This may be taken in conjunction with the finding of Mason (1964) that 95 per cent. of patients with Reiter's disease have prostatitis (defined as 10 pus cells per high power field in wet films made from prostatic secretion). He found prostatitis in 83 per cent. of patients with spondylitis and in 33 per cent. of patients with rheumatoid arthritis.

A genetic factor was first suggested by Morton (1958), who reported Reiter's disease arising independently in two cousins, by Csonka (1958), who reported that two brothers living in different parts of the country were affected, and also by Gough (1962). Csonka carried out a systematic enquiry regarding rheumatic disease in the first-degree relatives of 109 patients with Reiter's syndrome; 13 per cent. of these patients gave a clear account of rheumatoid arthritis in their families compared with 2 per cent. of a group of patients with uncomplicated non-specific urethritis or gonorrhoea. Csonka (1958) and also Laird (1958) have compared Reiter's disease with rheumatic fever and have suggested that urethral or intestinal infection triggers off the attack of arthritis only in predisposed individuals.

Method

Index cases for this survey were collected by members of the Cooperative Clinical Group of the Medical Society for the Study of Venereal Diseases in those V.D. clinics throughout the United Kingdom which were associated with a rheumatism centre. They included all white patients attending these centres in the period April 1, 1960, to March 1, 1964, in whom a diagnosis of Reiter's disease was made. The patient was asked if he would be willing for his family to be included in a family survey of the rheumatic diseases by the Arthritis and Rheumatism Council Field Unit. If he agreed, he was asked for the names and addresses of his living grandparents, parents, spouse, siblings, and children, and for the age at death and place and cause of death of such relatives if deceased. If the patient refused permission for his family to be examined, the number of living relatives was requested and these were included in the total sample.

A family study of venereal disease is beset with difficulties. Indeed it was only when the cooperation of rheumatologists was obtained and the emphasis shifted from Reiter's disease to arthritis that it became possible to obtain an adequate completion rate. The Reiter's disease survey thus became part of a general family study of rheumatic diseases with advantages which were both social and, as we shall see later, scientific.

All probands and their relatives aged 15 and over were asked to attend either the local hospital or a mobile unit and were subjected to a questionnaire on past rheumatism and arthritis and on diseases of the skin, eyes, and urinary system. A clinical examination of the musculo-skeletal system was carried out and a blood test and x rays of the hands, feet, and cervical spine were taken. In addition,

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the sacroiliac joints and hips were *x*-rayed in all males and in females aged 45 and over, and the lumbar spine and knees in all persons over the age of 34.

X rays were mixed with those taken from population samples in Leigh and Watford and with those from other family studies and read blind.

The blood serum was tested for rheumatoid factor by the sheep cell agglutination test (SCAT) by Dr. John Ball of Manchester University.

Completion rate

The survey was completed in 1967, when over 90 per cent. of the probands and their relatives had been examined, but data are available to us only on those seen up to 1964. Thus only probands and relatives living north of Leeds and a number in the Manchester area have been included in the present report. This is unfortunate since, owing to the small numbers, some of the findings fail to achieve significance. However, the impression gained by research workers taking part in the survey is that the later findings confirmed those reported here.

Of the 101 probands, 35 lived in this area, one had died, and 65 lived outside the area (Table I). Of the 35, one was found to have rheumatoid arthritis and has been excluded, together with his family, from the subsequent Tables. Sufficient data were available on the dead patient to permit of his inclusion. There were thus 35 probands, of whom twenty still had definite disease at the time of the survey (Table II, overleaf), three had only doubtful changes, and twelve had made a complete recovery. Seven had had symptoms of up to 6 months' duration but nine had symptoms for more than 5 years.

Radiological evidence of erosive arthritis was found in the hands or feet in 14 per cent. and sacroiliitis in 23 per cent. When the probands were divided according to the duration of symptoms, it was found that, of those with a history of up to 5 years, three (12 per cent.) had erosive arthritis in the hands or feet compared with 22 per cent. of those who had had the disease for a longer period. Sacroiliitis was present in two (8 per cent.) of those with a history of up to 5 years and five (71 per cent.) of those with a history of more than 5 years. All those with Grade 3–4 change in the sacroiliac joints fell into the latter category.

All probands had urethritis when first diagnosed in the V.D. clinic. In addition thirteen are known to have had conjunctivitis and three iritis. On the rest information is incomplete.

Of the 360 relatives, 110 had been examined at the time of this report. Of the 45 spouses, twenty had been examined. Of the relatives, six were grandparents, 32 were parents, 58 were siblings, and fourteen offspring; 47 of the relatives were male and 63 female.

Results

RHEUMATOID ARTHRITIS

Clinical evidence of rheumatoid arthritis was found in only two of the relatives compared with 4·8 expected (Table III). In both it was minimal (grade 2). Of the twenty spouses one had arthritis compared with 0·7 expected. Four male and six female relatives gave a history of past polyarthritis, compared with 6·4 expected. Of the twenty spouses, two gave a past history of polyarthritis.

Radiological evidence of erosive arthritis was present in the hands or feet in five relatives and in the cervical spine in five. It was minimal in all and there was no significant difference between relatives and controls. Only one of the spouses had erosive changes in the hands or feet and none in the cervical spine. None of the relatives or spouses had a positive sheep cell agglutination test.

SPONDYLITIS

The prevalence of ankylosing spondylitis, diagnosed clinically, radiologically, and by the Rome Criteria

TABLE I *Completion rate in Reiter's disease family study in December*, 1964

Series		*Completion rate*				
		Total	*Died*	*Not yet seen*	*Examined*	*Refused examination*
Probands	Males	100	1	64	35	—
	Females	1	—	1	—	—
	Total	101	1	65	35	—
Relatives	Males	162		109	47	6
	Females	198		128	63	7
	Total	360		237	110	13
Spouses	Males	1		1	—	—
	Females	44		24	20	—
	Total	45		25	20	—

TABLE II *Reiter's disease probands, clinical and radiological status*

Examination		*Grade of change*							*Not x-rayed*	*Duration (yrs) of arthritis Grade 2 to 4 in probands*					
		Total	0	1[a]	2	3	4	*Percentage* 2–4		$-\frac{1}{2}$	−1	−3	−5	−10	20+
Clinical status	Reiter's disease (present grade)	35	12	3	16	4	—			4	4	2	2	5	3
	Initial grade in those now grade 0–1	15	—	—	1	14	—			3	6	5	0	1	0
	Maximum grade	25	—	—	17	18	—			7	10	7	2	6	3
Radiology	Erosive arthritis Hands and feet Total	35	27	3	3	1	1	14							
	Up to 5 yrs duration	26	22	1	2	1	—	12							
	> 5 yrs duration	9	5	2	1	—	1	22							
	Erosive arthritis Cervical spine Total	34	31	1	2	—	—	6	1						
	> 5 yrs duration	9	8	—	1	—	—	11							
	Sacroiliitis Total	31	18	6	4	2	1	23	4						
	Up to 5 yrs duration	24	16	6	2	—	—	8	2						
	> 5 yrs duration	7	2	—	2	2	1	71	2						
Keratoderma		35	31	2	2			6							

[a]Grade 1 changes were doubtful

TABLE III *Inflammatory polyarthritis in relatives and spouses*

Findings		*Grade of arthritis*									
		Relatives						*Spouses*			
		Total examined	2	3	4	*Expected* 2–4	*Expected* 3–4	*Total examined*	2	3	4	*Expected* 2–4	*Expected* 3–4
Clinical	Present	110	2	0	0	4·8	1·2	20	1	0	0	0·7	0·06
	Past	110		10			6·4	20		2			1·4
Radiological	Hands or feet	110	5	0	0	4·2	0·6	20	1	0	0	0·4	0·03
	Cervical spine	108	5	0	0	3·8	0·4	20	0	0	0	1·2	0·02

(1963), in the relatives in our survey is compared in Table IV with the findings in a survey of spondylitis families undertaken by the Arthritis and Rheumatism Council and with a control population sample in the town of Watford. The prevalence of both clinical and radiological evidence of spondylitis was very similar in the two family groups and was two to eight times as great as in the controls. None of the spouses showed any evidence of spondylitis. Though the differences between relatives and controls were significant in the case of the spondylitis families, they failed to reach accepted levels of significance in the Reiter's disease families because of the small numbers examined.

PSORIASIS

As a family study of psoriatic arthritis was run concurrently with the Reiter's survey, we have compared the relatives in these two surveys with control population samples in Leigh, Wensleydale, and Watford in Table V. It will be observed that, whereas 13 per cent. of the male relatives in the Reiter's disease families had psoriasis, 12 per cent. of those in the psoriasis families had this disorder compared with an expected rate of 1 per cent. The difference between male relatives and controls is highly significant in both the Reiter's disease and psoriasis families ($P < 0{\cdot}01$). In the female relatives there was psoriasis in 2 per cent. of the Reiter's disease families

TABLE IV *Spondylitis in relatives and spouses of Reiter's disease and spondylitis probands*

Series examined					*Reiter's disease families*			*Spondylitis families*			*Controls*		
					Total	*Affected*		*Total*	*Affected*		*Total*	*Affected*	
						No.	*Per cent.*		*No.*	*Per cent.*		*No.*	*Per cent.*
Clinical spondylitis			Relatives	Male	47	2	4	133	6	4	202	1	0·5
				Female	63	0	0	117	2	2	218	0	0·0
			Spouses		20	0	0	50	0	0	50	0	0·0
Radiological changes	Sacroiliitis	Unilateral	Relatives	Male	43	6	14	128	26	20	123	7	6
				Female	25	3	12	60	5	8	67	1	1·5
			Spouses		4	0	0	25	0	0	66	1	1·5
		Bilateral	Relatives	Male	43	5	12	128	19	15	123	6	5
				Female	25	1	4	60	4	7	67	1	1·5
			Spouses		4	0	0	25	0	0	66	1	1·5
	Spine	Cervical	Relatives	Male	47	1	2	123	1	0·8	196	3	1·5
				Female	61	0	0	117	0	0	209	1	0·5
			Spouses		20	0	0	50	0	0	209	1	0·5
		Lumbar	Relatives	Male	27	1	4	83	6	7	83	1	1
				Female	29	1	3	79	4	5	88	0	0
			Spouses		10	0	0	41	0	0	88	0	0
Rome criteria 4+			Relatives	Male	43	2	4	128	4	3	123	1	0·8
				Female	25	0	0	60	1	2	67	0	0·0
			Spouses		4	0	0	25	0	0	66	0	0·0

TABLE V *Comparison of families of probands with Reiter's disease and psoriatic arthropathy*

Proband's diagnosis	*Sex of relatives*	*Reiter's disease families*		*Psoriatic arthritis families*		*Controls*	
		Total no.	*Affected (per cent.)*	*Total no.*	*Affected (per cent.)*	*Total no.*	*Affected (per cent.)*
Psoriasis	Male	47	13[a]	34	12[a]	1,426	0·9[a]
	Female	63	2	38	5	1,544	0·8
Clinical spondylitis	Male	47	4	34	3	1,426	0·5
	Female	63	0	38	0	1,896	0·05
Sacroiliitis	Male	43	14	30	7	123	6·0
	Female	25	12	27	3	67	1·5
Clinical polyarthritis	Male	47	4	34	9 [b]	1,318	3 [b]
	Female	63	0	38	8	1,535	5

[a]$P < 0·01$; [b]Difference significant for males and females combined; $P < 0·05 > 0·01$

and 5 per cent. in the psoriasis families compared with 1 per cent. in the controls.

Clinical spondylitis similarly had a higher prevalence in the male relatives in both surveys but none was found in the female relatives. Although the findings are suggestive, the number of men examined was too small for the differences to be statistically significant. *X*-ray evidence of sacroiliitis did not show the same increase in the psoriasis families who, however, had significantly more clinical polyarthritis than the controls ($P < 0·05$). Only one of the relatives, a male relative of a patient with Reiter's disease, had definite psoriatic arthritis. Of the seven Reiter's disease relatives with psoriasis, two were relatives of a proband with grade 2 keratoderma. One other proband had grade 2 keratoderma but none of his relatives had psoriasis.

Discussion

The first point which must be determined in any family survey is whether any aggregation discovered

is genuine or spurious. Observer bias has been excluded as far as possible by mixing relatives from a number of family studies. Some sixteen family surveys were run synchronously with the Reiter's disease family study. The proband's diagnosis was kept from the physician till he had made his diagnosis in the relatives and was not thereafter changed. Moreover the *x* rays were mixed not only with those from the other family surveys but also with control *x* rays taken from random population samples.

Another possibility which must be excluded is selection bias. If more than one member of a family is affected there is a greater chance that the family will be included in the survey, as pointed out by Smith (1959). In no instance have two cases of Reiter's disease been encountered in the same family in this survey.

If the familial aggregation of spondylitis and psoriasis is genuine, how is it caused ? The completely negative results in the spouses would appear to be against the family environment as the cause unless this operates in childhood. The small number and the sex of the spouses, however, may have hidden a genuine environmental influence.

It may be considered whether, as spondylitis is a common late sequel of Reiter's disease (Good, 1961) and about the same proportion of relatives of Reiter's disease and spondylitis probands have clinical spondylitis or radiological sacroiliitis, Reiter's disease may be an early stage of ankylosing spondylitis, triggered by an infection of the urinary tract. It seems clear from the findings of Mason (1964) and others that prostatic inflammation is frequent in ankylosing spondylitis even if it is not overt.

This is supported by the finding of Grimble (1963) of antibodies to prostatic antigens in both diseases, and although his suggestion that an autoimmune mechanism may be responsible cannot be accepted without reserve, his findings do at least indicate that cell damage with release of cell-bound antigens is occurring in the prostate. The absence of sacroiliitis in the majority of Reiter's patients, however, would appear to be against the concept that it is identical with ankylosing spondylitis. It should be pointed out, however, that five out of seven of those with a history of more than 5 years had sacroiliitis, and its absence in the early cases may simply indicate that radiological changes have not yet developed. The transient involvement of peripheral joints in the early stage also does not exclude this hypothesis. Attacks of polyarthritis have been noted by Hollister and Engleman (1958) as a frequent precursor of spondylitis. Against this hypothesis is the absence of keratoderma blennorrhagica in spondylitis and the finding of a high prevalence of psoriasis in relatives of patients with Reiter's disease but not in relatives of spondylitic patients, only 2 per cent. of whom had psoriasis. This would seem to provide a link with psoriatic arthritis.

Kulka (1962) observed that the mechanism of tissue damage in Reiter's disease might possibly be analogous to that in psoriasis, since not only is it capable of producing skin lesions which are indistinguishable, but also these lesions can be provoked in a similar manner by local physical irritation. Weinberger (1962) recorded the evolution of Reiter's cutaneous lesions into what appeared to be cutaneous psoriasis, and Pindborg, Gorlin, and Hansen (1963) reported that the buccal lesions in Reiter's disease, raised slightly red areas 1 to 10 mm. in diameter on the buccal mucosa, closely resemble pustular psoriasis histologically. Porrini, McEwen, Ditata, Poppel, and Lingg (1964) noted a close resemblance between Reiter's disease and psoriatic arthropathy on the basis of the involvement of peripheral, sacroiliac, and other joints, pelvic and parapelvic structures, and paravertebral calcification. The nail changes of psoriasis have also been noted in Reiter's syndrome (Weinberger, Ropes, Kulka, and Bauer, 1962).

From their total experience of psoriatic arthritis, Wright and Reed (1964) described twelve cases which they considered to demonstrate an intimate link between psoriatic arthritis and Reiter's syndrome. These patients developed keratoderma blennorrhagica and psoriasis and the two appeared to be related temporally and histologically. The high incidence of ocular manifestations and sacroiliac joint involvement emphasized the lack of demarcation between Reiter's syndrome and psoriatic arthritis.

Thus Reiter's disease may be an early stage of psoriatic arthritis appropriately triggered by a urogenital infection. The absence of rhematoid serum factors is a further point of similarity. The absence of rheumatoid arthritis in the Reiter's disease relatives but a suggestive increase in frequency of arthritis in the psoriatic arthritis families would make this less likely. A possible explanation is that patients with Reiter's disease carry traits associated with both spondylitis and psoriasis. Psoriasis by itself is not associated with a genetic predisposition to arthritis. In a series of 92 first degree relatives of patients with skin psoriasis examined by the Arthritis and Rheumatism Council Field Unit, no case of rheumatoid arthritis more severe than grade 1 was encountered. The age and sex distribution was such that arthritis would have been expected in a significant proportion. Thus it would appear that persons developing psoriatic arthritis have both psoriatic and arthritic traits if a genetic cause is accepted. This is analogous to the findings in Still's disease, in which

evidence of both a spondylitic and arthritic trait may be involved (Ansell, Bywaters, and Lawrence, 1962).

Summary

110 relatives and twenty spouses of 35 patients with Reiter's disease have been examined clinically and have had *x* rays of the hands, feet, spine, and pelvis, and a sensitized sheep cell test for rheumatoid factor. Comparison was made with relatives of patients with ankylosing spondylitis and psoriatic arthritis, and with population samples in Leigh, Wensleydale, and Watford examined in the same way.

Rheumatoid arthritis and rheumatoid factor were not more frequent in the Reiter's disease families than in the population samples.

Psoriasis was fourteen times more common in male relatives of Reiter's disease patients than in the general population and was as frequent as in the psoriatic arthritis families.

Clinical ankylosing spondylitis was eight, and radiological bilateral sacroiliitis nearly three times as frequent in the male relatives in Reiter's disease families as in the population and had almost the same frequency as in the spondylitis families. These findings are suggestive but, owing to the small number of relatives in the Reiter's disease families, not statistically significant.

Psoriasis and spondylitis were not found in the spouses. It is concluded that heredity plays an important part in predisposing infected individuals to develop Reiter's disease, and that there is a genetic association with psoriasis and possibly with ankylosing spondylitis.

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Enquête familiale dans la maladie de Reiter

SOMMAIRE

110 parents et 20 conjoints de 35 malades atteints de maladie de Reiter furent examinés cliniquement et par radiologie des mains, des pieds, de la colonne vertébrale et du pelvis; on pratiqua également une recherche du facteur rhumatoïde à l'aide des cellules de mouton sensibilisées. Une comparaison fut faite avec des parents de malades atteints de spondylite ankylosante et d'arthrite psoriasique ainsi que sur des échantillons de population à Leigh, Wensleydale, et Watford, examinés de la même manière.

L'arthrite rhumatoïde et le facteur rhumatoïde ne furent pas trouvés plus fréquemment dans les familles de sujets atteints de maladie de Reiter que dans les échantillons de population.

Le psoriasis fut quatorze fois plus fréquent chez les parents mâles des malades atteints de maladie de Reiter que dans la population générale et fut aussi fréquent que dans les familles de maladies atteints d'arthrite psoriasique.

Une spondylite ankylosante clinique fut huit fois, et des signes radiologiques de sacro-iliite bilatérale furent presque trois fois, aussi fréquents chez les parents mâles de sujets atteints de maladie de Reiter que dans la population et eut presque la même fréquence que dans les familles spondylitiques. Ces constations sont suggestives mais, du fait du petit nombre des parents dand les familles à maladie de Reiter, elles ne sont pas statistiquement significatives.

Le psoriasis et la spondylite ne furent pas trouvés chez les conjoints. On conclut que l'hérédité joue un rôle important en prédisposant les individus infectés à presenter une maladie de Reiter et qu'il y a association génétique avec le psoriasis et peut-être avec la spondylite ankylosante.